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Lambda Light Chain Crystalline Cast Nephropathy and Proximal Tubulopathy

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INTRODUCTION

Plasma cell dyscrasias such as multiple myeloma (MM) result from clonal proliferation of plasma cells and subsequent overproduction of Igs, including free light chains. Renal dysfunction is a core manifestation of plasma cell dyscrasias. A broad range of kidney pathologies can occur, including light chain cast nephropathy, monoclonal Ig deposition disease, light chain amyloidosis, light chain proximal tubulopathy, and tubulointerstitial nephritis.[1–3]

Light chain proximal tubulopathy (LCPT) is a rare manifestation of monoclonal gammopathy and is characterized by the accumulation of monotypic light chains within the proximal tubule epithelial cells. The accumulated light chains frequently form crystals; however, noncrystalline forms of LCPT have been described.[4,5] LCPT with crystals is associated with a kappa light chain in the vast majority of cases, which is discovered by either routine immunofluorescence (IF), IF, or immunohistochemistry after protease digestion of the paraffin-embedded tissue. LCPT without crystals can be seen with both kappa- and lambda-restricted disease. When crystals are present, ultrastructural examination is often essential to the diagnosis as crystals may be easily missed by light microscopy. The diagnosis of LCPT is of great clinical importance. In up to 85% of patients, kidney biopsy showing LCPT is the initial clue to an underlying plasma cell dyscrasia before a diagnosis has been established or the disease has come to clinical attention.[5] Therefore, the diagnosis of LCPT is crucial for appropriate patient management. We report an unusual case of LCPT in a 59-year-old woman associated with lambda light chain restriction with prominent intraluminal crystalline casts.

CASE PRESENTATION

A 59-year-old Caucasian woman presented with weakness, fatigue, and acute kidney injury with signs of marked dehydration. She had a history of left-sided nephrectomy 6 years ago due to a large staghorn calculus. Fifteen months before presentation, she was diagnosed with MM after presenting with anemia, fatigue, multiple lytic bone lesions, and serum protein electrophoresis showing an M-spike with monoclonal IgA lambda. Bone marrow biopsy revealed 90% clonal plasma cells with a high-risk cytogenetic profile. She was treated with bortezomib, dexamethasone, and lenolidomide with good response and bone marrow biopsy 6 months after her initial diagnosis showed no residual myeloma; however, positron emission tomography scan demonstrated persistent bony disease.

At the time of her acute presentation, serum creatinine was 3.8 mg/dl with an estimated glomerular filtration rate of 13 ml/min per 1.73 m^2 calculated by the 4-variable Modification of Diet in Renal Disease study equation. Quantitative urine protein measurements revealed nephrotic-range proteinuria with 4 g per 24 hours. Urine electrolyte studies were not performed. I.v. fluid resuscitation failed to improve her renal function, and because of significant proteinuria and concern over persistent MM, kidney biopsy was performed.

Kidney Biopsy

Twenty glomeruli were sampled, all of which were patent and without significant pathologic alterations. Proximal tubules demonstrated diffuse loss of brush borders, extensive cytoplasmic vacuolization, and sloughing of cell cytoplasm into tubular lumina. Focally, proximal tubular epithelial cells showed prominent intracytoplasmic inclusions, some of which were sharply demarcated and rhomboid in appearance (Figure 1a). These inclusions were brightly eosinophilic on the hematoxylin and eosin stain, pale on the periodic acid Schiff stain, and fuschinophilic on the trichrome stain (Figure 1b). In addition, tubules frequently showed large intraluminal collections of

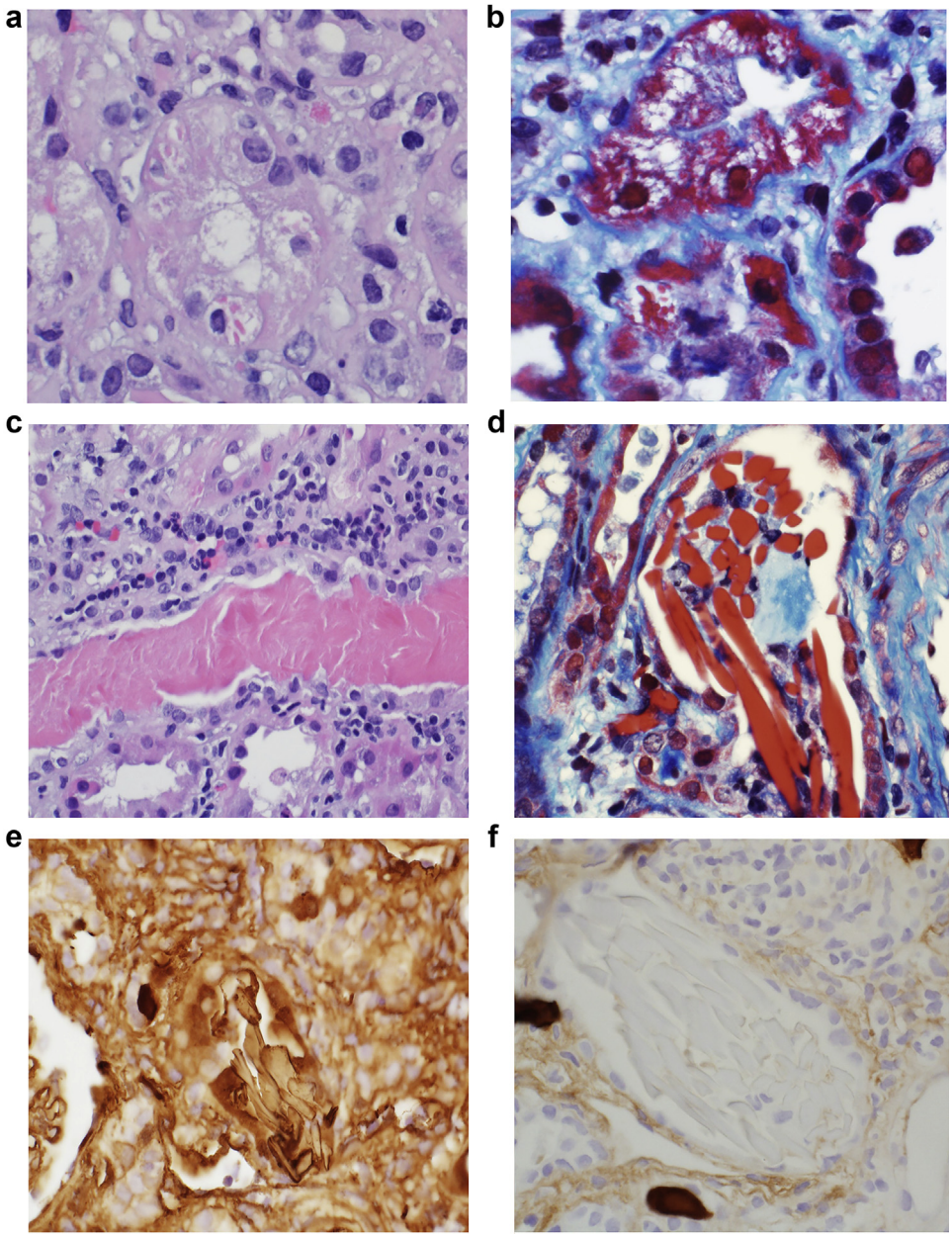

Figure 1. (a) Proximal tubules show prominent injury with coarse cytoplasmic vacuolization and brightly eosinophilic intracytoplasmic inclusions (hematoxylin and eosin). (b) Intracytoplasmic inclusions were fuschinophilic on the trichrome stain (trichrome). (c) Numerous intraluminal casts were seen, some of which showed a fine fibrillary structure (hematoxylin and eosin), whereas (d) others demonstrated needle-like and rhomboid crystals (trichrome). Immunohistochemical stains for a (e) lambda light chain and (f) kappa light chain highlighted prominent light chain restriction within luminal casts and cytoplasmic material.

needle-shaped and rhomboid structures, many of which were associated with an inflammatory reaction (Figure 1c and d). There was no birefringence under polarized light. There was a diffuse and mixed interstitial inflammatory infiltrate consisting primarily of mononuclear cells with scattered neutrophils and rare eosinophils. The degree of interstitial fibrosis and tubular atrophy was moderate, involving up to 40% to 50% of the sample. Mild chronic vascular disease was observed without features of arteritis.

By direct IF microscopy, there was no glomerular staining for IgG, IgA, IgM, C3, C1q, kappa light chain, lambda light chain, fibrinogen, or albumin. The intratubular casts and cytoplasmic inclusions showed weak staining for a lambda light chain without staining for a kappa light chain. Because of weak staining, immunohistochemical studies for kappa and lambda light chains were performed, which revealed strong staining of the intratubular and intracytoplasmic material for the lambda light chain without staining for

the kappa light chain (Figure 1e and f). Ultrastructural examination of glomeruli showed no abnormalities. The evaluation of the tubules revealed abundant intraluminal crystalline structures with both needle-like and rhomboid configuration (Figure 2a). Focally, proximal tubular epithelial cells showed large prominent electron dense inclusions (Figure 2b). Overt crystal formation was not seen within proximal tubular cells. Substructural organization was not observed.

Biopsy Diagnosis

The biopsy was interpreted as acute tubular injury and/or necrosis with light chain crystalline cast nephropathy and proximal tubulopathy (lambda light chain restricted).

Clinical Follow-up

After her acute presentation and kidney biopsy findings, the patient deferred further therapy for her MM and initiated comfort care. She subsequently passed away from her disease 16 days after kidney biopsy was performed.

DISCUSSION

Light chain proximal tubulopathy is a rare manifestation of MM that results from both overproduction and abnormal production of light chains by neoplastic plasma cells. Prior studies have shown an estimated biopsy incidence of 0.5% to 5% in patients with a monoclonal gammopathy.[3–5] Under normal conditions, proximal tubular epithelial cells reabsorb small volumes of free light chains through the megalin and/or cubulin receptor, which are endocytosed and trafficked to the lysosomes for degradation.[6] In patients with paraproteinemia, the reabsorptive capacity of the proximal tubules may be overwhelmed by the increased volume of light chains, leading to Bence-Jones proteinuria and accumulation of pathogenic light chains within proximal tubule epithelial cells. Also contributing to the disease process are atypical biochemical properties of these light chains. The light chain variable domain is impervious to breakdown by lysosomal enzymes, which leads to accumulation in renal tubular epithelial cells.[7,8] Furthermore, these abnormal light chains can have an intrinsic propensity to crystallize.[9] Light chain crystals can also accumulate in other cell types such as podocytes and macrophages, disease processes termed light chain podocytopathy and crystal storing histiocytosis, respectively.[10–12]

In addition, crystalline cast nephropathy can be a complication of plasma cell dyscrasias and has only rarely been reported in the setting of LCPT. In most cases, the crystalline casts take on similar morphologic features to the intracytoplasmic crystals.[5] In the described case, overt crystal formation was not seen within proximal tubular cells; however, widespread crystalline casts were seen obstructing distal tubules. This combination of findings shows the dynamic nature of these particular pathogenic light chains with crystallization in distal nephron segments, likely owing to alterations in the surrounding milieu and interaction with uromodulin (Tamm-Horsfall protein).

Crystalline LCPT is almost exclusively seen in kappa-restricted disease with only rare examples of lambda-restricted intracytoplasmic crystals.[4,13] The presence of crystalline casts is regarded as uncommon in LCPT and their presence is typically only a focal finding. Haider *et al.*[14] reported a patient with acute kidney injury resulting from lambda-restricted intraluminal crystalline casts; however, concurrent LCPT was not observed.

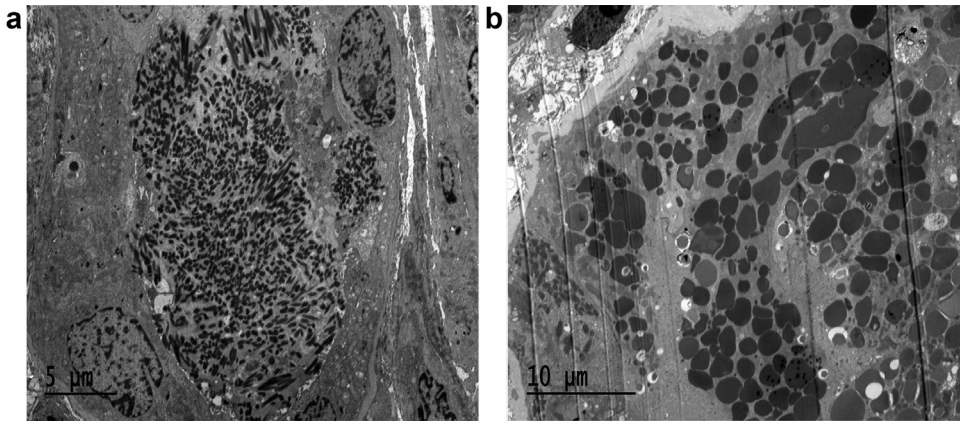

Figure 2. (a) Ultrastructural examination revealed abundant intraluminal crystalline casts. (b) Focally, prominent intracytoplasmic electron dense inclusions were present within proximal tubular epithelial cells.

LCPT without crystals has also been reported, and these cases are more likely to be lambda restricted than crystalline LCPT. Noncrystalline LCPT may result from light chains that do not have the biochemical propensity to crystallize.[4,5] In some cases without crystals (particularly those without clinical evidence of kidney injury or Fanconi syndrome), the light chain accumulation may simply be due to physiological uptake by proximal epithelial cells and may not represent pathogenic tubular injury.

The diagnosis of LCPT can be challenging, and is made by the identification of light chain-restricted intracytoplasmic inclusions within the proximal tubule epithelial cells, which may be quite focal.[5] They typically stain brightly eosinophilic on the hematoxylin and eosin stain, pale on the periodic acid Schiff stain, and fuschinophilic on the trichrome stain. In the largest series of such cases, Stokes *et al*. reported 46 cases of LCPT (40 with crystals and 6 without). All 40 cases with crystals were kappa light chain restricted, whereas 2 of 6 noncrystalline forms were lambda light chain restricted. Nine cases demonstrated intraluminal crystalline casts, which were only focally present, and were associated with crystalline LCPT.[5] Larsen *et al*. reported 13 patients with light chain proximal tubulopathy. One patient with lambda-restricted disease showed rare intracytoplasmic crystals by electron microscopy, and intraluminal crystalline casts were not mentioned.[4]

When evaluating a biopsy with prominent intraluminal casts or crystals, the differential diagnosis is broad. Intraluminal casts that stain brightly eosinophilic on the hematoxylin and eosin stain include cases of light chain cast nephropathy, myoglobinuric- or hemoglobinuric-associated tubular injury, casts associated with mechanistic target of rapomycin (mTOR) inhibitory toxicity, and bile cast nephropathy.[15–18] Intraluminal crystals can be seen in a wide variety of conditions including primary or secondary oxalosis, phosphate nephropathy, drug toxicity (particularly foscarnet and indinavir), and 2,8 dihydroxyadeninuria. In the case of oxalosis, the crystals are typically rhomboid in shape, yellow in color, and are birefringent under polarized light. Crystals associated with foscarnet and indinavir are best seen on frozen sections and are also polarized. On electron microscopy, these crystals appear as cleared out spaces, unlike the markedly electron dense crystals seen in light chain-associated disease. The crystals of 2,8 dihydroxyadeninuria are often brown in color, needle to rhomboid in shape, and are birefringent when viewed under polarized light.[19–21]

In LCPT, IF studies may highlight light chain restriction in the proximal tubule epithelial cells. In cases with crystals, routine IF microscopy on frozen tissue may show false-negative results. In such cases, utilization of IF on paraffin-embedded tissue after digestion with protease better highlights the light chain restriction.[22] Immunohistochemical studies can also be useful, as in our case. Electron microscopy is of paramount importance in cases of LCPT and can highlight intracytoplasmic and intraluminal electron dense crystalline structures as well as enlarged atypical lysosomes. Occasionally, substructural organization, such as paracrystalline arrays, can be seen.[5]

Clinically, patients with LCPT may present with acquired Fanconi syndrome characterized by normoglyemic glycosuria, aminoaciduria, hyperphosphaturia, and type II renal tubular acidosis.[5,8,23] Slowly progressive chronic renal failure may occur and recurrence after transplant has been reported.[24] The International Kidney and Monoclonal Gammopathy Research Group recommends chemotherapy or stem cell transplant for LCPT even before worsening hematologic disease occurs.[25] Treatment of the underlying plasma cell dyscrasia in patients with LCPT has shown varying results with a minority in one study showing complete response, while most patients had stable hematologic disease. Kidney function showed a general trend toward improvement in patients who were treated either with chemotherapy alone or with chemotherapy and stem cell transplantation.[5] Furthermore, renal involvement is an independent predictor of poor outcomes in MM,[26] and the early identification of LCPT may help stratify risk and drive patient management.

In summary, LCPT is a rare but important finding on renal biopsy and requires a high index of suspicion and thorough investigation of the sample, often including immunohistochemical studies or IF after protease digestion on the paraffin-embedded tissue. Correct diagnosis is crucial in driving proper patient management including chemotherapy and/or stem cell transplant for both control of the hematologic process and treatment of kidney disease, particularly in patients who require transplantation.

DISCLOSURE

All the authors declared no competing interests.

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